

PATENT ABSTRACTS OF JAPAN

D4

(11)Publication number : 07-275344
(43)Date of publication of application : 24.10.1995

(51)Int.Cl.

A61L 27/00

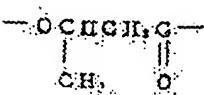
(21)Application number : 05-090534
(22)Date of filing : 05.04.1994

(71)Applicant : NIPPON ZEON CO LTD
(72)Inventor : NOISSHIKI YASUHARU
KOMATSUZAKI SHIGERU

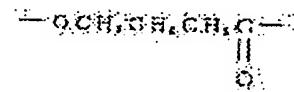
(54) MEDICAL MATERIAL FOR SOFT TISSUE

(57)Abstract:

PURPOSE: To provide a material with high bio-compatibility and prevent problems on the safety such as cytotoxic effect, etc., by composing the material with fiber aggregate and polyester copolymer with a 3-hydroxybutylate unit and a 4-hydroxybutylate unit shown by the specific formulae.



CONSTITUTION: A medical material for soft tissue consists of fiber aggregate and polyester copolymer with 3-hydroxybutylate shown by the formula I and 4-hydroxybutylate shown by the formula II. This medical material for soft tissue has good decomposition and absorption to biomedical tissue, and holds the designated shape even after decomposition and absorption. The copolymer is covered by the tissue as it penetrates into the biomedical tissue and the decomposition and absorption of this material gradually progresses by the action of the tissue. Even in a case fiber aggregate consisting of a material with a strong foreign matter reaction such as polyglycolic acid, etc., the decomposition and absorption of the copolymer into biomedical tissue is good and it suppresses the foreign matter reaction with biomedical tissue.



LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision
of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

Copyright (C) 1998,2000 Japanese Patent Office

BEST AVAILABLE COPY

* NOTICES *

The Japanese Patent Office is not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. *** shows the word which can not be translated.
3. In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] this invention relates to the medical-application material for tissues suitable for an artificial blood vessel, an artificial skin, the suture for an operation, synchia prevention material, the vessel restorative dental materials, etc.

[0002]

[Description of the Prior Art] This organization is asked for decomposition absorption being carried out according to irruption of a biodegradability, i.e., a body tissue, besides safeties, like there are not dynamic fitting, such as flexibility and an intensity, and toxicity in the medical-application material for tissues used for an artificial blood vessel, an artificial skin, the suture for an operation, synchia prevention material, the vessel restorative dental materials, etc.

[0003] Since the aliphatic polyester used for the suture for an operation etc., such as a polyglycol acid and a polylactic acid, lacks in flexibility, its fitting with the organism which is rich in flexibility is bad. Therefore, along with a motion of the organism, a mechanical stimulus arises in the interface with the organism. Moreover, since it decomposed regardless of irruption of a body tissue by the adding-water resolvability, the repair nature of a body tissue could not be followed, but the dissonance arose between body tissues, and there was a fault, such as triggering an inflammatory reaction in the organism.

[0004] since the activity (antigenicity) of the antigen-antibody reaction triggered by the material of other animals, such as a foreign protein, in order to control the decomposition absorption to this organization according to irruption of a body tissue is reduced, or in order that animal origin materials, such as a collagen used for an artificial skin etc., gelatin, and a chitin, may control superfluous decomposition, they need to construct a bridge and the problem of the cytotoxicity by moreover a cross linking agent remaining produces them -- there was a fault of a grade.

[0005] the example of the medical-application material for tissues which combined knitting or textiles, and the animal origin material *** -- bridge formation of gelatin or a collagen -- the artificial blood vessel to which the blinding of polyester-fiber knitting or the textiles was carried out by the object is known however, bridge formation of gelatin or a collagen -- since there is no elasticity in an object, the whole artificial blood vessel becomes hard and flexibility is spoiled, when it elongates too much, inflexible collagen and gelatin may exfoliate from knitting etc. Moreover, there was a trouble of a grade where there was a problem of the cytotoxicity by a cross linking agent remaining.

[0006] Furthermore, the prosthetic dentistry material for organism organum which the laminating of the permeable layer of non-absorptivities, such as the porous-structure field which consists of knitting or textiles of polyester etc., and the non-water permeability layer which contains at least the absorptivity material layer which consists of a polyglycol acid, a polylactic acid, etc. is carried out as an example of the medical-application material for tissues which combined knitting or textiles, and aliphatic polyester, and made this *** the side in contact with the sanguis is proposed (JP,2-208457,A). However, when a blood coagulation object separates on a front face for non-water permeability, it becomes inadequately discharging this prosthetic dentistry material of the body fluid out of a blood coagulation object, and a blood coagulation object accumulates it. Moreover, since this material was non-water permeability, there was a trouble where the adhesive property with a body tissue was missing. Moreover, even if it optimized composition of an absorptivity material layer and it optimized the absorption term to a body layer. Therefore, the result it should not necessarily be satisfied of the result with the artificial skin which consists of these prosthetic dentistry material, or an artificial blood vessel is not obtained.

[0007] On the other hand, various properties, such as a biocompatibility, the suture nature with a body tissue, elasticity, and flexibility, are required of the vessel restorative dental materials used for the patch for an artificial blood vessel, the heart, and vessel etc.

[0008] If polyester-fiber knitting or textiles did not make the spacing of fiber small in order to prevent a leakage of the sanguis although excelled in the suture nature with a body tissue, they was difficult to apply to the patch for the heart and vessel. Therefore, polyester-fiber knitting or large, make the sanguis touched just before use and a thrombus is made to form in the mesh of a fiber clearance, although there is the technique of carrying out a blinding by absorbents in the living body, such as the technique of carrying out a blinding by this or a collagen, and gelatin, if 10% or more of extensibilities is in a base material, a blinding will separate, and the danger of bleeding is conceived.

[0009] The medical-application composite-construction object which consists of the polyvinyl alcohol or the vinyl alcohol system copolymer and elasticity fiber knitting which have a crosslinking bond, or textiles is excellent in the biocompatibility in a damp or wet condition, elasticity, and flexibility, and it is known that it is suitable for an artificial blood vessel etc. (the JP,4-1631,B 1st *** of 2-13 lines, this 3rd *** of 18-24 lines). However, since this medical-application composite-construction object remained, without decomposing polyvinyl alcohol and the vinyl alcohol system copolymer with a possibility which elasticity and flexibility are not demonstrated in the dryness usually used since it is fundamentally formed from the quality of the material of water swelling nature, but is hard to deal with it that the introductory process of a crosslinking bond may cause the cytotoxicity by complicated survival of a cross linking agent in the living body, it had the problem that the organization by irruption of a body tissue was not good etc.

[0010]

[Problem(s) to be Solved by the Invention] A biocompatibility, elasticity, and flexibility are good, and do not cause the problems on safe, such as a cytotoxicity, but the purpose of this invention has them in the point of offering the new medical-application material for tissues which canceled the above-mentioned trouble.

[0011]

[Means for Solving the Problem] It is related with the medical-application material for tissues characterized by consisting of a polyester copolymer which has the 4-hydroxy butyrate unit shown by the 3-hydroxy butyrate unit shown by the aggregate and the following formula (1) of fiber, and the following formula (2) the first of this invention.

[0012] The second of this invention is related with the artificial blood vessel or vessel restorative dental material's characterized by being formed

- of the above-mentioned medical-application . . . fit for tissues.
- [0013] (fiber aggregate) The fiber aggregate of this invention can be the laminating field by knitting, textiles, the nonwoven fabric, networks, or such arbitrary combination.
- [0014] Especially the material and character of fiber that constitute the structure of the fiber aggregate which constitutes the medical-application material for tissues of this invention, and the aggregate are not restricted. As an example of such a material, material; of *** non-organism terephthalate of the organism absorptivity like poly-dioxa non, polyether ester, polyurethane, nylon, rayon, polypropylene, a polytetrafluoroethylene, a gossypium, and silk, is mentioned. Also of it, the viewpoint of fitting with a body tissue to polyester is desirable, and especially a polyethylene terephthalate is desirable also of polyester.
- [0015] Although what has elasticity is desirable as for the fiber aggregate, that in which the elastic ductility of at least 1 orientation has 20% or more of elasticity preferably 10% or more is suitable for the fiber aggregate used especially for an artificial blood vessel and the vessel vessel or the vessel restorative dental materials in forming an artificial blood vessel and the vessel restorative dental materials. When it uses for an artificial blood micrometers preferably are usually suitable for the spacing between each fiber of the fiber aggregate in respect of the organization by insertion of a body tissue. Although especially the character of fiber is not restricted, the thing of about 0.01-50 deniers of sizes is desirable on a manufacture of knitting or textiles.
- [0016] The biodegradability polyester copolymer which constitutes the medical-application material for tissues of this invention is the following formula (1).
- [Formula 3]
- $$\begin{array}{c} \text{O} \text{CH}_2 \text{C} \text{H}_2 \text{C} \text{---} \\ | \quad || \\ \text{CH}_2 \quad \text{O} \end{array} \quad \cdots \cdots \quad (1)$$
- The 3-hydroxy butyrate (henceforth 3HB) unit come out of and shown, and the following formula (2)
- [Formula 4]
- $$\begin{array}{c} \text{O} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{C} \text{---} \\ || \\ \text{O} \end{array} \quad \cdots \cdots \quad (2)$$
- It is the copolymer which comes out and has the 4-hydroxy butyrate (henceforth 4HB) unit shown (this copolymer is called below 3HB and 4HB polyester copolymer). 3HB and 4HB polyester copolymer receive a zymolysis by the lipase esterase which exists in a body tissue, and does not remain in the living body.
- [0017] A manufacture of 3HB and 4HB polyester copolymer which constitutes the medical-application material for tissues of this invention is not limited exceptionally that what is necessary is to just be based on technique better known than the former. The typical manufacture technique of 3HB and 4HB polyester copolymer For example, the - of one line 4th page upper-right *** of 18 lines of the 2nd page lower-right *** of JP,64-48021,A, The - of two lines 4th page upper-left *** of four lines of the 2nd page lower-left *** of JP,1-222788,A, The - of 11 lines 4th page upper-left *** of 17 lines of the 2nd page lower-left *** of JP,1-304891,A, It is indicated by the - of two lines 4th page upper-left *** of three lines of the 2nd page lower-left *** of JP,2-27992,A, the JP,4-326094,A 2nd *** of 19 lines -, the 3rd *** of 39 lines, the JP,4-326932,A 2nd *** of seven lines -, and the 4th *** of two lines.
- [0018] A culture medium or the nitrogen of culture medium, and/or Lynn are restricted and cultivated under presence of the carbon source and citric acid which serve as the substrate of hydroxy butyrate in the biomass which has hydroxy butyrate polymer production ability, and a copolymer is made to accumulate in a biomass in these well-known typical technique. In addition, you may perform the preceding paragraph
- [0019] As an example of the above-mentioned biomass, it is Alcaligenes. ***** (ATCC0750), Alcaligenes A rpus run day (ATCC15749), Alcaligenes ***** (ATCC29712), Alcaligenes ***** (ATCC14400), Alcaligenes Alcaligenes, such as ***** (ATCC17698), are mentioned. A culture medium will not be restricted especially if a biomass is the matter which can carry out a utilization. As the example, mineral salt; like a yeast extract, a poly-peptone, the inorganic nitride; phosphoric-acid hydrogen sodium like a saccharide; ammonium sulfate like a natural-product; glucose like a meat extract; a phosphoric-acid hydrogen potassium, and a magnesium sulfate is mentioned.
- [0020] As an example of the compound used as a carbon source used as the substrate of hydroxy butyrate, it is mineral salt; gamma-butyrolactone; following general formula HO(CH_n)_nOH of the above-mentioned butyric-acid derivatives, such as butyric-acid derivative 4-hydroxybutyric-acid sodium like 4-hydroxybutyric acid and 4-***** butyric acid. (n= 2, 4, 6, 8, 10, 12) It comes out and aliphatic diols; expressed is mentioned. although especially the amount used is not restricted - desirable - 3-100g / l - it is especially referred to as 3-50g/l preferably 4HB unit content of 3HB and 4HB polyester copolymer is changeable by changing the amount used. Generally, if the amount used increases, 4HB unit content will tend to become high.
- [0021] In order to obtain the polyester copolymer which contains 4HB unit beyond abbreviation 60 mol % especially, it is desirable to add a citric acid and/or a citrate to an incubation system. As an example of a citrate, a specific salt, potassium salt, and an ammonium salt are mentioned. although the amount of a citric acid or a citrate changes with the strain of the used microorganism, desired copolymer composition, etc. - a culture medium or 1L of culture medium -- receiving -- usually -- 0.3-40 -- it is about [1-30g] preferably about g The amount of the copolymer obtained if there is too much amount used decreases.
- [0022] When the preceding paragraph incubation for proliferating a biomass in advance of the incubation for polyester generation is performed Carry out separation recovery of the biomass of a microorganism by filtration and the usual solid-liquid-separation means like a centrifugation from the culture medium obtained by incubation of the preceding paragraph, and in " which gives the collected biomass to latter incubation Or this culture medium can be made to shift to latter incubation, without making nitrogen and/or Lynn drained substantially in incubation of the preceding paragraph, and carrying out separation recovery of the biomass.
- [0023] For example, separation recovery of the biomass is carried out, and this biomass is washed, it dries by usual solid-liquid-separation means, such as filtration and a centrifugation, and a dried cell is obtained from the culture medium obtained by the incubation for polyester generation. 3HB and 4HB polyester copolymer are obtained from this dried cell by extracting 3HB and 4HB polyester copolymer by the organic solvent like chloroform or an acetone, adding a poor solvent like a hexane to this extract, and settling a copolymer by the conventional method.
- [0024] the preceding paragraph incubation performed by the incubation for polyester generation, and the case - setting - pH -- usually -- 6-10 -- it is preferably referred to as 6.5-9.5, and cultivates aerobically A dissolved oxygen concentration usually sets 0.5-40 ppm to 5-20 ppm preferably. About 20-40 degrees C of incubation temperature are usually preferably made into about 25-35 degrees C. it is not advantageous to the amount of polyester which carries out a generation stops becoming very low in a dried cell, and manufacturing industrially when these conditions are removed and cultivated.

[0025] 4HB unit content of 3HB and 4HB poly - copolymer which constitutes the medical-application material for tissues of this invention - usually -- 30-99 mol % -- desirable -- 40-96 m. -- it is 60-95 mol % especially preferably The decor. According to irruption of a body tissue becomes slow too much, and the effect of this invention is not fully acquired except that flexibility and elasticity will fall, if the content of 4HB unit is too low. If too high, flexibility and elasticity will become a fall inclination. the content of 3HB unit -- usually -- 1-70 mol % -- desirable -- 2-60 mol % -- it is 5-40 mol % still preferably Moreover, 3HB and 4HB polyester copolymer may have monomer units other than 4HB and 3HB unit, the content of monomer units other than 4HB and 3HB unit -- usually -- 30 mol % -- desirable -- less than [20 mol %] -- it is less than [10 mol %] still preferably

[0026] moreover, the melting point of 3HB and 4HB polyester copolymer -- usually -- 37-185 degrees C -- desirable -- 40-180 degrees C -- further -- desirable -- 45-170 degrees C and molecular weight -- usually -- about 20,000-5,000,000 -- desirable -- 50,000-2,000,000 -- it is 100,000-1,000,000 (polystyrene standard sample reduced properly by the gel-permeation-chromatography method) more preferably II molecular weight is too small, elasticity will fall, and if too large, a manufacture of the medical-application material for tissues will become difficult. Structural stabilities, such as an artificial blood vessel which will consist of a medical-application material for tissues if the melting point is too low, become bad, and if too high, a manufacture of the medical-application material for tissues will become difficult.

[0027] The medical-application material for tissues of this invention consists of the fiber aggregates, such as knitting or textiles, and 3HB and 4HB polyester copolymer. Usually, the medical-application material for tissues of this invention may be only that to which 3HB and 4HB polyester copolymer intervene between fiber, although a part of fiber aggregate [at least] is covered by 3HB and 4HB polyester copolymer, the medical-application material for tissues of this invention -- setting -- the weight proportion of the fiber aggregate, and 3HB and 4HB polyester copolymer -- the fiber aggregate 100 weight section -- receiving -- 3HB and 4HB polyester copolymer -- usually -- 0.1 - 1000 weight section -- desirable -- 0.5 - 500 weight section -- it is 1 - 300 weight section still preferably As technique of obtaining the medical-application material for tissues of this invention, 3HB and 4HB polyester copolymer of the solution status are used, and technique to carry out freeze-drying processing of immersing and xeranis processing, immersing and poor-solvent processing, and the frame mold use for the fiber aggregate etc. is mentioned. In this case, other components in the domain by which the purpose of this invention is not spoiled if needed may be included in the solution. The method of pasting both up using the organic solvent or adhesives as an example of the art which used 3HB and 4HB polyester copolymer of the melting status, where the film or powder of technique or this copolymer which heats the film or powder of 3HB and 4HB polyester copolymer in the status that knitting or textiles was made to contact, beyond the melting point of this copolymer is contacted on knitting or textiles is mentioned.

[0028] the technique with above-mentioned very common immersing and xeranis processing -- it is -- the copolymer concentration of the immersion fluid in the case of this invention -- 0.01-30(w/v) % -- desirable -- 0.1-10(w/v) % -- it is 0.2-5(w/v) % especially preferably In addition, % (w/v) of a unit expresses more than in g of the solute which is soluble in a 100ml solvent.

[0029] Above-mentioned immersing and poor-solvent processing are the technique of pulling and continuing end processing by the poor solvent, after performing above-mentioned immersing and xeranis processing, the processing temperature in a poor solvent -- completely -- a limit -- there is nothing -- low temperature, a room temperature, and an elevated temperature -- any are sufficient As a poor solvent, alcohol, such as hydrocarbons, such as a hexane and a cyclohexane, a methanol, ethanol, and an isopropanol, or water can be mentioned.

[0030] Freeze-drying processing of frame mold use is the technique of freeze-drying, after immersing the fiber aggregate in the above-mentioned immersion fluid of a copolymer. If freeze drying can be dried, with the freeze status maintained, there is especially no limit, usually, the solvent which can melt a copolymer in -20 degrees C - a room temperature grade with the melting point preferably will be used, and -50 degrees C - 50 degrees C of a dioxane, benzene, etc. will be mentioned as an example of such a solvent. A freezing point is usually about liquid nitrogen temperature -50 degrees C], throws dry ice into ethanol and is performed on the about [temperature -10 degree C] conditions of ethanol when the lump of dry ice remains into ethanol, the porous structure acquired if the porous structure acquired will become precise in many cases if it freeze-dries after freezing quickly as a general inclination, and it is made to freeze slowly and it freeze-dries -- rough -- ** -- there are many cases Moreover, in order to control structure, a specific field can be contacted on the cooling field and only a specific field can also be made into the structure different from others. The degree of reduced pressure is carried out in order to dry quickly, although there is no big influence in the porous structure acquired if xeranis is the temperature conditions of the domain which a freeze object does not dissolve, in the case of the dryer of a plate formula, 5 or less Torrs of 2 or less Torrs of the temperature of a plate are preferably carried out near the melting point of a solvent, or beyond the melting point as 1 or less Torr still preferably, and it dries in many cases.

[0031] As the technique of making it into porous structure, immersing and poor-solvent processing, How to process in the solvent which produces the copolymer processing object in the status that the specific solvent was made to distribute a ***** particle in the solution of a polyester copolymer in freeze-drying processing, and melts this particle, and does not melt a copolymer, and carry out the lysis elimination only of this particle. Although there is the technique of using together the technique of making contain a foaming agent and fabricating it or such technique etc., since the material of the porous material with high flexibility and elasticity is obtained, especially freeze-drying processing is suitable.

[0032] Although especially the thickness of the medical-application material for tissues of this invention is not restricted, from the viewpoint of quick elimination of the foreign matter in the living body by attaining decomposition absorption for a short time, and suppression of a side effect, 1000 micrometers or less are desirable and especially 50 micrometers or less are desirable. However, if a part or all of structure of this material is made into porous material even if it is in the case that thickness is large, decomposition absorption can be performed for a short time.

[0033] The medical-application material for tissues of this invention has the good decomposition absorption to a body tissue, and a configuration predetermined also in after decomposition absorption is held. 3HB and 4HB polyester copolymer are covered by this organization in connection with irruption of a body tissue, and the device is presumed for decomposition absorption of 3HB and 4HB polyester copolymer to advance quietly by operation of this organization. Moreover, since the decomposition absorption to the body tissue of 3HB and 4HB polyester copolymer is good even if a polyglycolic acid etc. is the case where the fiber aggregate which consists of a strong material of a foreign matter reaction is used, the foreign matter reaction with the organism is suppressed.

[0034] When the medical-application material for tissues of this invention is sutured among the chorion deficit section in the cavum abdominis, the medical-application material for tissues is covered by the body tissue, and a chorion is reproduced after this organization. And the medical-application material for tissues of this invention decomposes into healing of a chorion deficit gradually from a front face with this material by operation of a wrap body tissue, finally it is absorbed by the body tissue, and the aggregate of fiber is covered by the body tissue.

[0035] The medical-application material for tissues of this invention is used suitable for an artificial blood vessel, an artificial skin, the suture for an operation, synechia prevention material, the vessel restorative dental materials, etc.

[0036] (an artificial blood vessel or vessel restorative dental materials) The above-mentioned medical material for tissues comes to form the artificial blood vessel and vessel restorative dental materials of this invention. The medical material for tissues is usually preferably distorted to less than 10% of asymmetry in the tension test of at least 1 orientation, and the artificial blood vessel or vessel restorative dental materials of this invention does not have the yield point to less than 20%. When it was distorted in the tension test of at least 1 orientation said here, it did not have the yield point to less than 10% and the tension test to various orientation is performed, it says that at least one orientation where the yield point does not exist in less than 10% of asymmetry, and the fracture point does not exist, either exists.

[0037] By the same technique as the technique of obtaining the medical-application material for tissue, after forming in the configuration of the requests of the aggregate of fiber as technique of obtaining the artificial blood vessel and vessel restorative dental materials of this invention, such as the shape of tubular and a sheet, after obtaining the technique or the medical-application material for tissues processed by 3HB and 4HB polyester copolymer, the technique of forming is mentioned. The technique of the viewpoint of the ease of carrying out of formation to the former is suitable.

[0038] The artificial blood vessel and vessel restorative dental materials of this invention usually have the water permeability of the grade which does not start ***. When the water permeability said here pours the water pressure of 120mmHg, it is an amount which water passes in 1 minute per two 1cm of wall surfaces. In order to prevent *** in the artery system and systemic-heart system with high blood pressure, in it, it is desirable that water permeability uses the following [100ml/cm²/min/120mmHg], and especially the thing for which the following [50ml/cm²/min/120mmHg] are used is desirable in it. It is desirable that water permeability, on the other hand, uses the thing beyond 100ml/cm²/min/120mmHg for the venation and a right-heart system from the viewpoint of formation of the inner membrane by expansion of a body tissue, and especially the thing for which the thing beyond 200ml/cm²/min/120mmHg is used is desirable.

[0039] Since the artificial blood vessel and vessel restorative dental materials of this invention make a front face a split face or raises water permeability, they can also be made into the shape of porous material etc. Thereby, the vessel restorative dental materials of this invention becomes the thing excellent in the adhesive property of the blood coagulation object in a vessel internal surface of parietal bone. In order to make a front face into a split face, usually, 3HB and 4HB polyester copolymer are made into a porous material configuration by the above-mentioned technique, or the spacing and size of fiber of knitting or textiles are adjusted.

[0040] In order to improve the handling nature when suturing with a body tissue, a surface active substance may be used for the artificial blood vessel and vessel restorative dental materials of this invention, and surface treatment by well-known technique may be performed to them. Phospholipid, such as lecithin, is mentioned as an example of the surface active substance used. As an example of the surface treatment technique, dipping processing by the phospholipid aqueous solution, dipping processing by the mixed liquor of aliphatic polyester and phospholipid, etc., are mentioned.

[0041] The artificial blood vessel and vessel restorative dental materials of this invention can be applied to the organism, without performing or performing pre *** processing by the sanguis, the fibrin paste, etc.

[0042] The artificial blood vessel and vessel restorative dental materials of this invention have the good organization by irruption of a body tissue. 3HB and 4HB polyester copolymer itself do not have foreign matter nature, since it is the zymolysis nature or the adding-water resolvability which this has in addition to the high thing of a cellular affinity, 3HB and 4HB polyester copolymer fraction decompose gradually by the contact to body fluid, and since it has moderate modulus elasticity and flexibility besides a body tissue invading in the produced opening, the ground is considered because physical fitting with a body tissue and a blood flow is good.

[0043] This artificial blood vessel and vessel restorative dental materials of this invention have a biocompatibility, elasticity, and good flexibility. Moreover, it excels in the handling nature when suturing with a body tissue. Since a maceration does not arise between an aliphatic polyester fraction and a base material even if it makes it extend 10% or more, handling nature is good and is low safe for the danger of bleeding. The artificial blood vessel and vessel restorative dental materials of this invention can be made into the shape of the shape of a sheet, and a straight pipe, and a bend, a tubular-with crimp grade, and arbitrary configurations according to a use site and the purpose.

[0044] When the vessel restorative dental materials of this invention created using tubular knitting or tubular textiles which attached the crimp is used, after aliphatic polyester decomposes and being absorbed by in the living body, the diameter of the vessel can be extended. Although an expansion of this path may be performed automatically (responding to growth of the organism for example) if needed for the organism, decision of a doctor can also perform it using the intracatheter with a balloon etc. Although the re-operation needed to be conducted according to growth etc., the number of times of the operation for exchanging artificial blood vessels can be stopped to the minimum extent by using the artificial blood vessel or vessel restorative dental materials of this invention.

[0045] The vessel restorative dental materials of this invention plays the role which absorbs the impact by the pulsation, when used for a blood vessel wall as the heart and a patch for vessel. Thereby, the thickening of turbulence and the neogenesis blood vessel wall, and adhesion thrombus layer of the blood flow of the heart and the vessel can be stopped.

[0046] The mode of this invention is shown below;

(1) The medical-application material for tissues which consists of a polyester copolymer which has the fiber aggregate and a 3-hydroxy butyrate unit, and a 4-hydroxy butyrate unit.

(2) The medical-application material for tissues of the above (1) whose 4HB unit content of above-mentioned 3HB and 4HB polyester copolymer is 30-99 mol %.

(3) The medical-application material for tissues of the above (2) whose above-mentioned 4HB unit content is 40-98 mol %.

(4) The medical-application material for tissues of the above (2) whose above-mentioned 4HB unit content is 60-95 mol %.

(5) The above (2), (3), or (4) medical-application materials for tissues whose number average molecular weight of above-mentioned 3HB and 4HB polyester copolymer is 20,000-5,000,000.

(6) The above (1) whose thickness is 1000 micrometers or less, (2), (3), (4), or (5) medical-application materials for tissues.

(7) The above (1) with porous structure, (2), (3), (4), (5), or (6) medical-application materials for tissues.

(8) The artificial blood vessel or vessel restorative dental materials which the melting point of 3HB and 4HB polyester copolymer becomes from the medical-application material for tissues of the above (1) which is 37-185 degrees C, (2), (3), (4), (5), (6), or (7).

(9) The artificial blood vessel or vessel restorative dental materials of the above (8) whose elastic ductility of the at least 1 orientation of the above-mentioned fiber aggregate is 10% or more.

(10) The artificial blood vessel or vessel restorative dental materials of the above (8) or (9) which is what has the spacing each fiber of whose which constitutes the above-mentioned fiber aggregate is about 5-5000 micrometers.

(11) The artificial blood vessel or vessel restorative dental materials of the above (9) or (10) whose size of the fiber which constitutes the above-mentioned fiber aggregate is 5-50 deniers.

(12) The artificial blood vessel or vessel restorative dental materials of the above (9), (10), or (11) which is the heart and a patch for vessel.

(13) The artificial blood vessel or vessel restorative dental materials characterized by being that to which the medical-application material for tissues is distorted in the tension test of at least 1 orientation, and does not have the yield point to less than 10%.

[Example] Hereafter, based on the example of reference, an example, the example of a comparison, and the example of an examination, this invention is explained concretely.

[0048] The example 1 (manufacture of 3HB and 4HB polyester copolymer) of reference

Culture-medium A(what melted 10g [of yeast extract] and poly-peptone 10g, 5g [of meat extracts], and 2(NH₄)₂SO₄ 5g in demineralized water, made 1L, and was adjusted to pH 7.0)200ml was put into the 2L flask, the biomass [the Alcaligenes ***** (ATCC17599)] was cultivated at 28 degrees C for 24 hours, and the centrifugation separated the biomass B.

[0049] 4g of a biomass B0 was made to suspend in 100ml of culture-medium B (what melted Na₂HPO₄ 4.4g, KH₂PO₄ 1.2g, NaCl 15.0g, and 5.0g of sodium citrate in demineralized water, made 1L, and was adjusted to pH 7.0) of culture-medium B. 100ml of this suspension was put into the 500ml Sakaguchi flask, it cultivated at 28 degrees C for 48 hours, and the centrifugation separated the biomass B1.

[0050] Distilled water washed the obtained biomass B1, the reduced pressure drying of this was carried out, and the dried cell Bd1 was obtained. Thus, heat-chloroform extracted the polyester copolymer from the obtained dried cell Bd1, after condensing an extract, it is dropped at a lot of hexanes, and the polyester copolymer was settled, it ****ed, this precipitation was dried, the polyester copolymer was separated, and 3HB and 4HB polyester copolymer were obtained.

[0051] For yield, as for -43 degree C and the melting point, 1.0g/1 and composition were [3HB and 4HB polyester copolymer / 4HB30%, 3HB20%, and Tg of 53 degrees C and number average molecular weight] about 500,000. In addition, composition It analyzed by 1H-NMR (solvent (1) CDCl₃), and the polystyrene standard sample reduced property by the gel-permeation-chromatography method showed number average molecular weight.

[0052] Replaced with example of reference 2 culture-medium B, and the amount of suspension was set to 50ml using culture-medium C (what was prepared like culture-medium B except not containing a sodium citrate), and also the biomass B0 was cultivated like the example 1 of reference, and 3HB and 4HB polyester copolymer were obtained. For yield, as for -11 degree C and the melting point, 1.1g/1 and composition were [this copolymer / 4HB50%, 3HB50%, and Tg of 51 degrees C and number average molecular weight] about 610,000. Composition and number average molecular weight were calculated like the example 1 of reference.

[0053] It replaced with example of reference 3 culture-medium B, and the amount of suspension was set to 500ml using culture-medium C (what was prepared like culture-medium B except not containing a sodium citrate), the 2000ml Sakaguchi flask was used, and also the biomass B0 was cultivated like the example 1 of reference, and 3HB and 4HB polyester copolymer were obtained. For yield, as for -9 degree C and the melting point, 1.2g/1 and composition were [this copolymer / 4HB20%, 3HB80%, and Tg of 163 degrees C and number average molecular weight] about 500,000. Composition and number average molecular weight were calculated like the example 1 of reference.

[0054] It is Rhizopus in the phosphoric-acid buffer solution about each copolymer obtained in the examples 1-3 of reference. The lipase (Seikagaku make) and Rhizopus originating in dextrin Decomposing all was checked when processed by the lipase (made in Mannheim) originating in arrhizus.

[0055] 200ml of 2(w/v) % chloroform solutions obtained by melting 4g of 3HB and 4HB polyester copolymer obtained in the example 1 of example of comparison 1 reference in 200ml chloroform was prepared, this thing was cast on the glass laboratory dish with a diameter of 15cm, chloroform was vaporized gradually, and the film with a thickness of about 200 micrometers was created. This film was cut for 4cm around, and the sample 1 was obtained.

[0056] The sample 2 was obtained like the example 1 of a comparison except having used 3HB and 4HB polyester copolymer obtained in the example 2 of example of comparison 2 reference.

[0057] The sample 3 was obtained like the example 1 of a comparison except having used 3HB and 4HB polyester copolymer obtained in the example 3 of example of comparison 3 reference.

[0058] 10ml of 2(w/v) % chloroform solutions of 3HB and 4HB polyester copolymer obtained in the example 1 of example 1 reference was prepared, this thing was cast on the glass laboratory dish with a diameter of 15cm, chloroform was vaporized gradually, and the film with a thickness of about 10 micrometers was created. A polyglycol acid mesh (***** mesh" type-number number #2, Davis+Geck, product made from Inc.) was put on this film, it processed for 30 minutes in 90 degrees-C oven in the status that it pressed down lightly from the top, a film and a polyglycol acid mesh were stuck; this thing was cut for 4cm around, and the sample 4 was obtained.

[0059] The polyglycol acid mesh used in the example of comparison 4 example 1 was cut for 4cm around as it was, and the sample 5 was obtained.

[0060] The sample 6 was obtained like the example 1 except having replaced with example of comparison 33HB, and 4HB polyester copolymer solution, and having used 2(w/v) % chloroform solution of a poly-caprolactone (product made from Aldrich).

[0061] The sample 7 was obtained like the example 1 of a comparison except having replaced with example of comparison 33HB, and 4HB polyester copolymer solution, and having used 2(w/v) % chloroform solution of poly (L-lactic acid) (product made from Polyscience).

[0062] The artificial blood vessel made from a polyester fiber a1 (the length of 7cm, and the bore of 8mm) of example 2 marketing A Pasteur pipette is used for Permeable:1200ml/cm²/min/120mmHg. It is made to sink in from the inside with 1(w/v) % chloroform solution of 3HB and 4HB polyester copolymer obtained in the example 1 of reference. Subsequently, it soaked into the hexane solvent, while 3HB and 4HB polyester copolymer in a chloroform solution were made to separate, chloroform was removed, and it dried in the nitrogen draft. The artificial blood vessel a2 which repeats operation of the above-mentioned chloroform solution sinking in - xeransis 3 times, and was processed by 3HB and 4HB polyester copolymer was obtained. Subsequently, the artificial blood vessel a2 was inserted in the rod made from Teflon (outer diameter of 8mm), a polyester mesh was twisted around the periphery of this artificial blood vessel a2, and it dipped into 3(w/v) % 1 of 3HB and 4HB polyester copolymer obtained in the example 1 of reference, and 4-dioxane solution, after freeze-drying this thing, it exfoliated and the polyester mesh of a periphery was removed from the rod made from Teflon, and the porous sample a3 was obtained. The water permeability of this sample a3 was 10ml/cm²/min/120mmHg. The rate of a percolation poured the water pressure equivalent to 120mmHg on the sample, and measured it by calculating the flow of the water for (per two) 1 minute 1cm of sample wall surfaces. When the sample a3 was observed by the scanning electron microscope, the polyester fiber, and 10-30 micrometers in thickness, and 3HB and 4HB polyester copolymer porous layer of 1-20 micrometers of apertures were unifying.

[0063] Using the rabbit with example of examination 1 weight of about 3kg, under pentobarbital sodium general anesthesia, the culminating section of the skin and the *** was carried out for the pars abdominalis after *** and disinfection, and eight chorion deficits of 3cm around were created at the antinode Kabeuchi side. Samples 1-6 were sutured among the chorion deficit section, and were sutured in the order of the malacotomy section and the skin section section. At this time, samples 4 and 6 applied the polyglycol acid mesh side to the chorion deficit section, and sutured it. Since it was hard, the sample 7 has not been sutured. Under anesthetization after ten weak feeding, blood removal death was carried out, and it made an incision in the abdomen and evaluated.

[0064] When each experiment site was evaluated with the naked eye, by the site which sutured the sample 5, synchia was observed between *** and the intestine. Synchia was not observed by the site which sutured other samples.

[0065] The cross section of each experiment site was observed in histology by hematoxylin-and-eosin dyeing. Consequently, by samples 1, 2, and 3, although the macrophage and the fibrocyte have pasted the front face of each sample, the whole has not decomposed completely 3HB and 4HB polyester copolymer only by only the surface fraction having decomposed.

[0066] As for the polyglycol acid mesh of a sample 4 (example 1), the periphery was covered by the body tissue, and it was observed that the whole has decomposed completely 3HB and 4HB polyester copolymer. Moreover, the chorion was being reproduced to the site which sutured the sample and the foreign matter reaction was also weak.

[0067] A foreign matter reaction is strong and the sample 5 of regeneration of a chorion was also partial.

[0068] Although, as for the polyglycol acid mesh of a sample 6, the periphery was covered by the body tissue, most poly-caprolactone sections

were not decomposed. Moreover, although was seen.

portion was being reproduced to the site which suture sample, the foreign matter reaction

[0068] Example of examination 2 sample a3 was cut to 5.5cm, and it transplanted to the thorax aorta of a crossbred adult dog. This transplant was able to be performed without pre **** processing. The bleeding from an artificial blood vessel wall surface did not accept. It was flexible, and the sample a3 was well adapted for the character and configuration of a flexible artery wall, and its suture nature was also good. Under anesthetization ten weeks after, blood removal death was carried out, and the thoracotomy was carried out and it evaluated. The probe patency of foremen ovale of the sample a3 was carried out good, and it was maintaining the function as aorta. As a result of observing in histology like the example 1 of an examination, irruption of the organization to a sample a3 is good, and it was observed that 3HB and 4HB polyester copolymer have decomposed almost extensively. Moreover, a foreign matter reaction is weak and inner-bark-ization was observed by sample a3 internal surface of parietal bone by the part.

[0070] After having judged knitting made from polyester (a horizontal knitted fabric plain stitch, 3 deniers, 250 micrometers of fiber spacing width, 500 micrometers long) whose example 3 elastic ductility is about 100% to 7x9cm and immersing into 2(w/v) % chloroform solution of 3HB and 4HB polyester copolymer, chloroform was vaporized on the glass laboratory dish with a diameter of 15cm, and knitting covered with 3HB and 4HB polyester copolymer was created. Similarly, 40ml of 2(w/v) % chloroform solutions of 3HB and 4HB polyester copolymer was cast on the glass laboratory dish, chloroform was vaporized gradually, and the film with a thickness of about 40 micrometers was created. Knitting covered with 3HB and 4HB polyester copolymer was put on this film, it processed for 30 minutes in 90 degrees-C oven in the status that it pressed down lightly from the top, and the vessel restorative-dental-materials sample 11 was obtained. When the sample 11 was observed by the scanning electron microscope (it is described as SEM below), it had become knitting and two layer structures of a film, and the field by the side of a film was smooth.

[0071] 3HB and 4HB polyester copolymer film side were turned down, and it put on the tray made from 15x13cm stainless steel, and in 90 degree-C oven, example 4 sample 11 was processed for 30 minutes, was cooled radially, and it was made to stick to a tray. 2(w/v) % 1 of 3HB and 4HB polyester copolymer and 19ml of 4-dioxane solutions were poured out on it, this thing was freeze-dried, and the vessel restorative-dental-materials sample 12 was obtained. When the sample 12 was observed by SEM, it has the three-tiered structure into which knitting is inserted between the film layer and the porous layer of about 100 micrometers of apertures, and the front face of a porous layer had turned into the split face and the field where the front face of a film layer is almost smooth.

[0072] The vessel restorative-dental-materials sample 13 was obtained like the example 4 except having used 2(w/v) % 1 used in the example 5 (product made from Wako pure medicine industry) 5% of the weight, and 4-dioxane solution. When the sample 13 was observed by SEM, it was the same structure as a sample 12.

[0073] The 7x9cm frame mold was created using aluminum material with an example 6 thickness of 1mm, it set so that 3HB and 4HB polyester copolymer film side might turn a sample 11 to this frame mold down, and as the spacing of 1mm was made between the bases of the tray made from 15x13cm stainless steel, it placed on this tray. 2(w/v) % 1 of 3HB and 4HB polyester copolymer and 38ml of 4-dioxane solutions were poured out on it, this thing was freeze-dried, and the vessel restorative-dental-materials sample 14 was obtained. When the sample 14 was observed by SEM, it had become the structure where knitting existed in the interval of a porous layer, and the porous layer by the side of about 10 micrometers of apertures and other fields of the porous layer by the side of the tray base made from stainless steel is about 100 micrometers of apertures, and each front face had turned into the split face.

[0074] The same knitting made from polyester as what was used in the example 7 example 3 was fused and fabricated by the heat sealer with a bore [of 12mm], and a length of 3cm in the shape of a spool, and it inserted in the glass U tube with an outer diameter of 10mm, heat-treated at 150 degrees C, and the knitting bend made from the polyester with a crimp a11 with a bore of 10mm was obtained. It was immersed into 2(w/v) % chloroform solution of 3HB and 4HB polyester copolymer, this bend a11 was inserted in the glass U tube with an outer diameter of 10mm, it dried in the nitrogen draft, and the knitting bend made from the polyester with a crimp a22 covered with 3HB and 4HB polyester copolymer was created. The periphery of a bend a22 was twisted in a polyester mesh, and subsequently to the inside of 2(w/v) % 1 of 3HB and 4HB polyester copolymer, and 4-dioxane solution it dipped, after freeze-drying this thing, it exfoliated and the polyester mesh of a periphery was removed from the glass U tube, and the vessel restorative-dental-materials sample 15 was obtained. When the sample 15 was observed by SEM, knitting made from polyester, and 3HB and 4HB polyester copolymer porous layer of 1-20 micrometers of apertures were unifying.

[0075] Knitting made from polyester which constitutes the example of examination 8 vessel restorative-dental-materials samples 11-15 and each sample was cut with a width of face of 20mm in the shape of a strip of paper, and it measured at 200mm of speed of testings, min, and the room temperature using the tension tester (TENSILON UTM-250, **** tech company make). In addition, all the **** orientation was made into longitudinal direction, and it asked for tensile stress as a load per test piece unit width of face. It asked for asymmetry as tensile strength when a sample destroys, and asymmetry at the time of tensile strength and a breakdown. A result is shown in Table 1.

[Table 1]

血管修復材 試料No.	11	12	13	14	15	ポリエステル 綾織物
至み10%での引張応力 (kg/mm)	0.65	0.64	0.62	0.63	0.63	0.65
降伏点での引張応力*) (kg/mm)	—	0.78	0.66	0.21	0.25	0.09
降伏点での至み*) (%)	—	210	170	130	150	100
引張強さ (kg/mm)	0.71	0.90	0.85	0.83	0.79	0.63
破壊時伸び (%)	240	250	240	230	230	250

The yield point did not exist by the notes * sample 11.

[0077] A part of ventriculus dexter of example of examination 4 dog was cut open, and the closed breast of the vessel restorative-dental-materials samples 11-14 cut suitably was sutured and carried out. Under anesthetization two weeks after, blood removal death was carried out, and the thoracotomy was carried out and it evaluated. In addition, by the sample 11, by samples 12 and 13, the suture made the porous-layer side of about 100 micrometers of apertures the sanguis side side for the porous-layer side by the sample 14, respectively, and performed the smooth copolymer film side. Each sample -- flexible -- flexible muscular Kabeuchi of the right heart -- it was well adapted for the character and the configuration, and suture nature was also good. Although the sample 13 was excellent in the water wettability, use for un-arranging did not have other samples.

[0078] When the status that the thoracotomy was carried out was evaluated with the naked eye, any sample was maintaining flexibility. Moreover, the reaction with any unusual sample was not seen.

[0079] Although the big blood coagulation lump formed on the smooth copolymer film by the side of a sanguis side by the sample 11 as a result of carrying out hematoxylin-and-eosin dyeing of the cross section of a sample and observing in histology with a light microscope, the irruption status of the organization from the outside to knitting made from polyester was good.

[0080] By samples 12 and 13, although the thin stable sanguis congelation layer forms on a porous layer and the organization according to irruption of an organization in a part of porous layer was beginning to occur, the organization had not invaded into a film layer.

[0081] By the sample 14, the thin stable sanguis congelation layer formed on the porous layer of about 100 micrometers of apertures, formation of the organization by irruption of the fibrocyte to a porous layer, a smooth valve cell, a capillary, etc. was also good, and inner-hair-ization called [internal surface] a wrap in an endothelial cell was also advancing. Moreover, decomposition of a copolymer had also started.

[0082] A part of pulmonary artery of example of examination 5 dog was excised, and it transposed to the vessel restorative-dental-materials wall which are rich in an extensibility, and its suture nature was also good. Under anesthetization two weeks after, blood removal death was carried out, and the thoracotomy was carried out and it evaluated. The sample 15 was maintaining the function as a pulmonary-artery spool. As a result of observing in histology like the example 4 of an examination, the thin stable sanguis congelation layer forms inside a pulmonary-artery spool, and the organization according to irruption of an organization in a part of porous layer is beginning to occur. Moreover, decomposition of a copolymer had also started.

[0083] From the ventriculus dexter of example of examination 6 dog, a bypass is made from the artificial blood vessel made tubular by the vessel restorative-dental-materials sample 15 to the pulmonary artery, next the origin section of an original pulmonary artery is ligated, and all pulmonary-artery blood was shed via the bypass. When the X-ray examination investigated the configuration of a bypass fraction three months after the thicket, the gestalt at the time of a thicket was kept good. Next, when the bore of a bypass is extended twice by the balloon attached at the nose of cam of a catheter, it can extend reasonable, and change was not accepted in a circulation moving state, either. When three months passed after that and the X-ray examination investigated the configuration of a bypass fraction again, the gestalt with an extended state was maintained. That is, it was able to act as the "student of 'the vessel restorative dental materials in which is grown up and it deals' and the body for arbitrary stage in arbitrary sizes by this material."

[0084] [Effect of the Invention] According to this invention, according to irruption of a body tissue, the medical-application material for tissues which decomposition absorption is carried out and was satisfied of dynamic fitting and safety with this organization is obtained. The medical-application material for tissues of this invention is used suitable for an artificial blood vessel, an artificial skin, the suture for an operation, synchia prevention material, etc. As a result of investigating by the cell culture, the medical-application material for tissues of this invention had the take of a cell, a move, and propagation better than the collagen layer. Especially the thing reformed by phospholipid, such as lecithin, etc. became still good. The artificial blood vessel or vessel restorative dental materials of this invention has a biocompatibility, elasticity, and good flexibility, and is excellent in the handling nature when suturing with a body tissue.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.